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Impact of the Introduction of A/Sydney/5/97 H3N2 Influenza Virus Into South Africa

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In 1998 South Africa experienced a major influenza epidemic that was characterized by extensive illness and an unusually early season. The impact of the epidemic was charted by measuring proxy indexes of influenza activity such as school absenteeism and excess mortality in persons older than 65 years. Viruses isolated from patients of all age groups were analyzed both antigenically and at the molecular level to determine the characteristics of the influenza strain responsible for the outbreaks. The study revealed that influenza activity was detected as early as the middle of April and peaked toward the end of May and early June. School absenteeism correlated with a sharp rise in virus isolation during this period. Consumption of influenza-related pharmaceuticals, as well as mortality figures, also corresponded to the increased absenteeism and virus isolation. Characterization of the viruses isolated during 1997 and 1998 showed clearly that the epidemic was caused by the introduction of the A/Sydney/5/97-like H3N2 influenza strain into South Africa in 1998. With no prior exposure to this virus strain, which is antigenically distinct from the viruses that had been present in this country in 1997, the population was highly susceptible, resulting in an early, rapid spread of influenza. This epidemic has highlighted the importance of having an influenza vaccine specifically formulated for the Southern Hemisphere. If the 1998 vaccine had not contained the A/Sydney/5/97 strain, the widespread outbreaks in South Africa would have been far worse in terms of morbidity, mortality, and economic loss. This, in turn, emphasizes the need for increased influenza surveillance and international cooperation. ***J. Med. Virol. 59:561–568, 1999.***

KEY WORDS: epidemic; disease; epidemiology; hemagglutinin; vaccine

INTRODUCTION

Influenza is a potentially serious viral respiratory disease associated with high morbidity and significant mortality. The seasonal epidemics that occur regularly are primarily due to continuous and unpredictable antigenic changes that take place in the viral surface hemagglutinin (HA) protein. Five major variable sites, designated A–E, have been defined on the globular head region of the HA protein, which is encoded by the HA1 subunit of the HA gene [Wiley and Skehel, 1987]. Mutations in these sites can give rise to an antigenically novel influenza virus that escapes the host's previously acquired immunity, which can then spread rapidly through a susceptible population.

Monitoring the antigenicity of the viruses in circulation each year is thus necessary to identify any new variant strains so that influenza vaccines with antigens closely matching those of the new strains can be prepared annually [Rota et al., 1992]. An active influenza surveillance program was established in 1984 at the National Institute for Virology (NIV) in Johannesburg to obtain virus isolates and to monitor influenza epidemics [Schoub et al., 1986]. Molecular characterization of local influenza virus isolates by sequence analysis of the viral HA1 subunit has also been carried out since 1993 to detect any new mutations relative to previous strains [Besselaar et al., 1996]. The influenza laboratories at NIV serve as one of the National Influenza Centers of the WHO and provide data annually to the Collaborating Centers for Reference and Research on Influenza.

Prior to 1998, the last major influenza outbreak in South Africa occurred in 1994, with the dominant strain being influenza B/Quingdao/102/91-like [Besselaar et al., 1996]. The outbreak peaked between the middle of June and July as measured by the increase in the number of isolates and sharp rise in school absenteeism [National Institute of Virology, 1994]. In con-

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trast, the influenza seasons for the period 1995 to 1997 were either mild or moderate [National Institute for Virology, 1995, 1996, 1997].

In 1998, South African experienced a major influenza epidemic—the earliest ever recorded with extensive morbidity and a marked increase in mortality. The dominant responsible influenza strain, A/Sydney/5/97 (H3N2), was not detected in South Africa in 1997. Its first isolation was in March 1998, apparently imported into the country from the Northern Hemisphere. The subsequent influenza epidemics could be charted by the National Institute for Virology by measuring proxy indexes of the severity of influenza and also by antigenic and molecular characterization of isolates derived from patients.

MATERIALS AND METHODS

Patients and Sources of Specimens

The active surveillance program of the South African National Institute for Virology consists of some 15 centers servicing a cross-section of the population residing mainly in the densely populated Gauteng province. These centers include general medical practitioners, pediatric outpatient departments at hospitals, a pediatrician, primary health care centers at several mines, a university clinic, and the staff clinic at NIV.

Patients were selected on the basis of clinical presentation of acute respiratory symptoms, rather than on the surveillance definition of influenza of the WHO [Assaad et al., 1973]. Throat swabs were taken from the patients within 48–72 hr of onset of symptoms and sent in viral transport medium to the NIV laboratories as described previously [Schoub et al., 1986].

In addition to the active surveillance program, influenza isolates were also obtained from routine diagnostic specimens sent for analysis for the presence of respiratory viruses. During the past 3 years, additional specimens were collected from infants hospitalized with severe acute respiratory infection at the Chris Hani/Baragwanath Hospital. This hospital is the largest in the world, servicing the population (estimated to be over 2 million) of Soweto, close to Johannesburg. A further source of influenza specimens was recruited from a baseline study for an antiviral clinical trial.

In this study, individuals of all age groups presenting with acute respiratory disease were sampled. Throat and nose swabs were collected from sentinal clinical practices between 4 May and 23 September. The majority of these practices were located in the Gauteng province while the remainder were from the Free State, North West, and Mpumalanga provinces. The climate in the study area is temperate, with an average temperature of 10.4°C in July in Johannesburg, the most populated city in Gauteng. In the summer, the temperature rises in Johannesburg to an average of 20.1°C in January [Anonymous, 1996].

Proxy Indexes of Influenza Activity

Proxy indexes of influenza activity were utilized to measure the extent and the impact of the epidemic. These include monitoring school absenteeism, the utilization of pharmaceuticals related to respiratory infections, and mortality in persons over 65 years.

School absenteeism has been monitored annually since 1987. In 1998, approximately 8,000 pupils at seven primary and two high schools were monitored. A weekly absenteeism rate per 1,000 pupils was calculated as described by Schoub et al. [1994].

An approximate measure of the utilization of pharmaceutical products in relation to influenza illness was obtained by estimating the winter excess in consumption of these materials. Data was obtained from the MedPharm database, a large company administering the utilization of pharmaceutical products by a large proportion of the private health industry in South Africa. A total of between 1.11 and 2.20 million items per month are stored in this registry. Those items classified as "cough and cold preparations" together with "antibiotics for systemic use" were counted and expressed as a percentage of all items, month by month for 1997 and 1998.

Mortality data was provided by the Johannesburg Jewish Burial Society (Chevra Kadisha), which is responsible for all Jewish burials in the greater Johannesburg area. Statistics were obtained of all deaths due to natural causes in individuals 65 years of age and older during 1997 and 1998.

Virus Detection by Shell Vial Assay

Specimens (0.2 ml) were inoculated in duplicate into shell vials that contained round coverslips (diameter 14 mm) seeded with MDCK cells 24 hr prior to the addition of the specimens. The treated shell vials were centrifuged (850 × g for 1 hr at room temperature), the inoculum aspirated off and replaced with 2 ml of fresh serum-free DMEM with 0.11% sodium pyruvate (Gibco BRL, Life Technologies), antibiotics and 2-μg/ml trypsin (TPCK, SigmaBiochemicals). The vials were incubated at 33°C for 40–48 hr and the cells fixed to the coverslips using 90% acetone. The coverslips were mounted onto the microscope slides using xylene mounting fluid. Immunofluorescence staining was carried out using the Light Diagnostics kit (Chemicon International, CA). The slides were air-dried, mounted with glycerol, and examined at a magnification of × 200 with a UV fluorescent microscope (Olympus BH2-RFCA).

Virus Isolation

Specimens were processed and inoculated intra-amniotically into 12-day-old embryonated eggs as described by Schoub et al. [1994]. Specimens were also inoculated into 24-well MDCK cell cultures in serum-free DMEM supplemented with 2.5-μg/ml trypsin and incubated for 3–5 days at 33°C. Chorio-allantoic or cell culture supernatants were tested for hemagglutination (HA) as outlined by Schoub et al. [1994], but using turkey red blood cells rather than fowl cells.

TABLE I. Sequencing Primers for Influenza A (H3N2) HA1 Gene

Primer	Nucleotides	Sequence
H3/1/1	48–62	5′-TGAGCTACATTTTAT-3′
H3/2/1	171–185	5′-GACCAAATTGAAGTG-3′
H3/3/1	361–376	5′-GCAACTGTTACCCTTA-3′
H3/4/1	669–683	5′-GCATCAGGGAGAGTC-3′
H3/5/1	858–872	5′-CGAAGTGGGAAAAGC-3′
H3/6/2	227–212	5′-TCTACCTGTTGAGGAA-3′
H3/7/2	766–742	5′-TTCTACTAGACAGACCCCTTACCC-3′

Antigenic Typing

Virus isolates in chorio-allantoic or tissue culture fluid were preliminarily typed by HA inhibition (HAI) with reference antisera supplied by the WHO Collaborating Center for Influenza, CSL, Melbourne. The antisera used for detecting H3N2 viruses were A/Sydney/5/97, A/Nanchang/933/95, and A/Wuhan/359/95. The HAI test was carried out according to the method outlined by Schoub et al. [1994], but using turkey red blood cells instead.

A sample of positive isolates were sent to Dr. Alan Hay of the WHO Collaborating Center for Influenza, NIMR, London, for further antigenic characterization by HAI with ferret antisera raised against various reference viruses. The postinfection ferret sera used for the H3N2 isolates included the following: A/Sydney/5/97, A/Bratislava/6/97, A/Nanchang/933/95, A/Wuhan/359/95, and A/Johannesburg/33/94. Antiserum raised against Resvir-13, the high growth reassortant vaccine strain for A/Sydney/5/97, was also included. Preseason influenza isolates were in addition tested against reference A/South Africa/1147/96 ferret antisera.

Molecular Characterization

Influenza A H3N2 viruses isolated during 1997 and 1998 in South Africa were analyzed by nucleotide sequencing of the HA1 subunit of the HA gene. The strains selected for genetic analysis were chosen to represent isolates obtained at the beginning, middle, and end of the 1997 and 1998 influenza seasons.

RNA was extracted from 140 μl of infectious tissue culture supernatant or allantoic fluid using the QIAamp Viral RNA extraction kit (Qiagen GmbH, Hilden, Germany). The amplification of the HA1 coding region by PCR was carried out using the conditions described previously [Besselaar et al., 1996]. The PCR products were 1,073 base pairs (bp) in size.

Prior to sequencing, the amplified products were purified by enzyme digestion using the PCR product presequencing kit (Amersham Life Science, Cleveland, OH). The purified DNA was sequenced using the Thermo-Sequenase radio-labeled terminator cycle sequencing kit supplied by Amersham Life Science. The oligonucleotide primers (Table I) were numbered according to the sequence of A/Aichi/2/68 HA cDNA [Verhoeyen et al., 1980]. Reaction products were separated on 8% polyacrylamide urea sequencing gels, and data were analyzed using the HIBIO DNASIS program (Hitachi Software Engineering Ltd, Brisbane, CA).

RESULTS

1997 Isolates

During 1997, 134 of the respiratory specimens received at NIV were positive for influenza as detected by the shell vial assay. The great majority of these positive samples were made from the Gauteng province (129/134) and the remaining 5 from the neighboring Mpumalanga province.

All the positive specimens were isolated and subtyped by HAI. Four specimens were found to be positive both for influenza A H3N2 and influenza B, i.e., dual infections, giving a total of 138 virus isolates. The majority of the isolates (77/138 or 55.80%) were influenza A H3N2, 10 were influenza H1N1 (7.24%), and the remaining 51 isolates were typed as influenza B (36.16%).

The first influenza A H3N2 isolate of the 1997 winter season was made from a specimen collected on 14 May and the last from a throat swab taken on 3 September. In addition to the winter isolates, two preseason H3N2 viruses were isolated; one on 20 January and the other on 11 March. Seven of the 10 H1N1 isolates were made from specimens taken from 25 July to 14 August. The remaining three H1N1 viruses were isolated in November. The first winter influenza B virus was isolated from a specimen taken on 7 July and the last from a specimen collected on 12 September.

The number of positive isolates from the various surveillance studies were as follows: 59/138 (42.75%) from the Chris Hani/Baragwanath Hospital, 44/138 (31.89%) from the Viral Watch Program and routine clinical specimens, and 35 (25.36%) from the baseline survey for the trial.

1998 Isolates

During 1998, 367 respiratory specimens sent to the laboratories were positive for influenza using the shell vial assay. Of these, 366 (99.7%) were identified as influenza A and only 1 as influenza B. The influenza specimens were mainly obtained from Johannesburg (195; 53.3%) and Pretoria (67; 18.3%) in the Gauteng province. Seventy-nine (21.6%) influenza A positives were made from Bloemfontein in the Free State province, while the remaining 25 (6.8%) came from the Mpumalanga and North West provinces. Virus isolates were obtained from 70 of the 366 influenza-positive specimens. These were subtyped by HAI and the majority (62/70; 88.6%) were found to be subtype H3N2.

Two preseason H3N2 isolates were made in Febru-

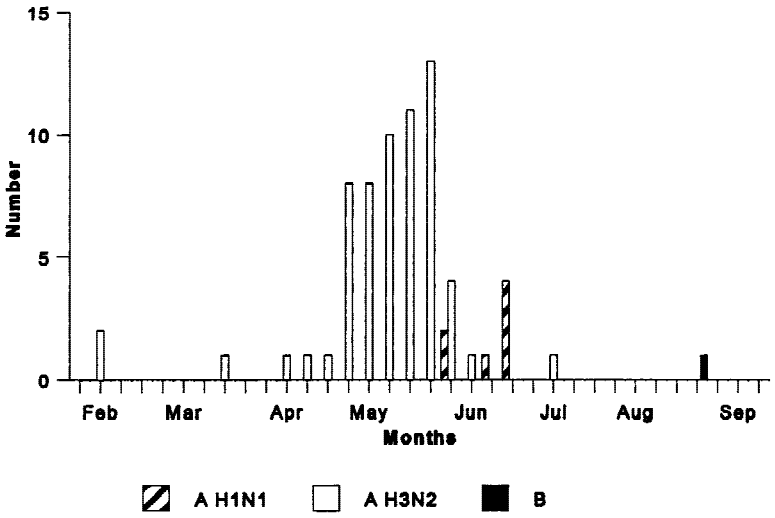

Fig. 1. Distribution of the 1998 subtyped influenza isolates.

ary and one in March. The March isolate, A/Jhb/3/98, was obtained from a Johannesburg resident who had recently returned from a visit to Thailand. The first H3N2 isolate of the influenza season was made from a specimen collected on the 9th of April and the last was from a specimen taken on the 13th of July. In contrast, the influenza A H1N1 viruses were all isolated during June and the first week of July, while the influenza B-positive specimen was collected from a patient in Johannesburg on the 4th of September.

The majority of the 1998 influenza A-positive specimens were obtained from the baseline surveillance for the antiviral trial (260/366; 71.0%). Fifty-two (14.2%) positives were from the Chris Hani/Baragwanath Hospital, 49/366 (13.4%) were from the Viral Watch Program, while only 5 (1.4%) were obtained from routine specimens.

Proxy Indexes of Influenza Activity

In 1997 the school absenteeism surveillance program did not show a rise above two standard deviations above the mean of the absentee rates over the past 5 years and consequently this influenza season in Gautent was reported as "relatively quiet" [Anonymous, 1998].

In contrast to the low influenza activity seen in 1997, there were widespread outbreaks of influenza throughout South Africa in 1998. The epidemic was unusually early with the first influenza isolate made on the 14th of April. Over the next few weeks the epidemic increased sharply, reaching a peak towards the end of May and early June (Fig. 1).

Unlike 1997, school absenteeism in 1998 rose to well above two standard deviations of the 5-year mean (Fig. 2). At the height of the epidemic, the absenteeism was 80 per 1,000. Consumption of influenza-related pharmaceuticals, as well as mortality figures, also corresponded to school absenteeism and influenza virus isolations (Fig. 3).

Antigenic Analyses

Antigenic subtyping by HAI revealed that the H3N2 isolates in 1997 reacted to high titer against both the A/Nanchang/933/95 and A/Wuhan/359/95 antisera. In 1998, subtyping of the 62 H3N2 isolates showed that the viruses reacted strongly with A/Sydney/5/97 antisera. The only exceptions were the two viruses isolated in February (A/Jhb/1/98 and A/Jhb/2/98), which reacted poorly with both A/Sydney/5/97 and A/Nanchang/933/95 antisera.

Representative 1997 H3N2 isolates sent to NIMR in London for antigenic characterization by HAI using postinfection ferret sera were all found to be antigenically similar to A/Wuhan/359/95 (Alan Hay, personal communication). Some of the isolates were also closely related to the more recent A/Bratislava/6/97 reference virus. Isolates made later in the season were also tested with antiserum raised against the A/Sydney/5/97 virus strain, but all showed reduced reactivity with this antiserum.

Antigenic characterization of the 1998 H3N2 isolates by HAI using ferret antisera revealed that all the viruses isolated from March onward reacted most strongly with A/Sydney/5/97 and Resvir-13. The two February isolates were not tested.

Molecular Analyses

Sequence analyses of the 1997 H3N2 isolates showed some amino acid differences relative to the A/Nanchang/933/95 vaccine strain. Two preseason isolates, A/Jhb/1/97 and A/Jhb/3/97 obtained from patients in January and March, respectively, had amino acid changes at residues 121 (threonine to asparagine), 124 (glycine to serine), and 133 (aspartic acid to asparagine), which are characteristic of the reference A/SA/1147/96 strain. These substitutions are shown in Table

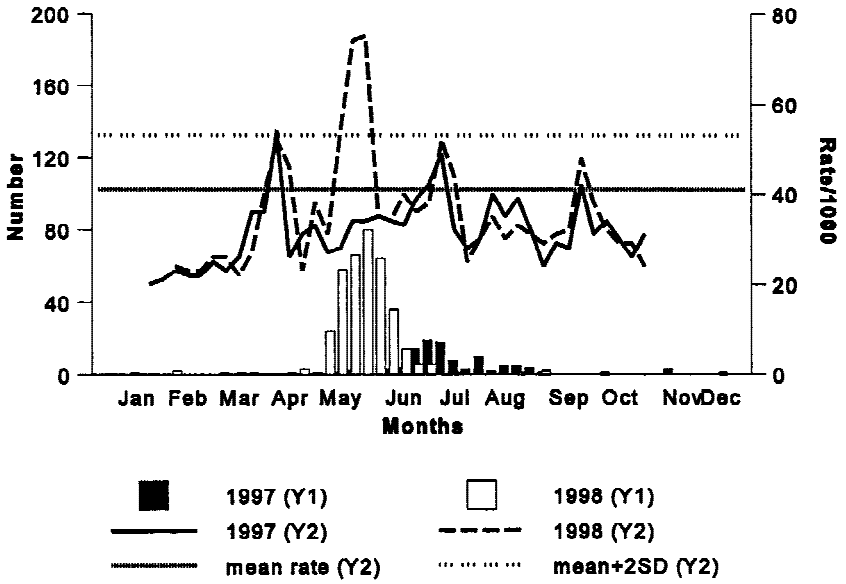

Fig. 2. Distribution of influenza isolates and school absenteeism for 1997 and 1998.

II, where A/Jhb/1/97 is compared with both the A/Nanchang/933/95 and A/SA/1147/96 strains. The first two H3N2 viruses of the winter season, isolated in May, also exhibited these differences at residues 121, 124, and 133, but had additional substitutions at residues 140, 142 and 190 (data not shown).

In contrast, H3N2 viruses isolated from June onward had changes at very different residues (Table III). All had identical substitutions relative to A/Nanchang/933/95 at residues 92 (lysine to threonine), 122 (asparagine to lysine), 216 (asparagine to serine), 226 (isoleucine to valine), and 275 (glycine to aspartic acid). The majority of these isolates also had glutamine instead of arginine at residue 57. Additional mutations were seen in some of the isolates as shown in Table III. The mutations at residues 57, 92, 122, and 275 are characteristic of the A/Bratislava/6/97-like variants, which evolved along on different lineage to the A/SA/1147/96-like viruses (Alan Hay, personal communication). The amino acid substitution seen in the majority of the South African isolates at residue 216 appears to be a unique change not observed in other A/Bratislava/6/97-like viruses.

Molecular characterization of the 1998 H3N2 isolates revealed that the two isolates made in February had identical amino acid sequences to the first virus isolated in January the previous year. A comparison of the amino acid residues of A/Jhb/1/98 with A/Jhb/1/97 is shown in Table II.

Sequence analyses of viruses isolated from March to July, on the other hand, showed that the isolates were A/Sydney/5/97-like. Amino acid differences between the South African isolates and the Sydney vaccine strain were observed for some residues (Table IV). Common changes between all the isolates and the A/Sydney/5/97 strain were found at residue 3 (isoleucine to leucine) and 142 (serine to arginine). Other substitutions seen in some of the South African isolates occurred at residues 103 (proline to glutamine), 194 (isoleucine to leucine), 226 (isoleucine to valine), 229 (arginine to glycine), and 289 (proline to serine). Two early isolates, A/Jhb/3/98 and A/Jhb/4/98, also exhibited a change at residue 186 (serine to isoleucine), while several later isolates had a substitution at position 137 from tyrosine to serine. One of the isolates (A/Jhb/44/98) was found to have glycine instead of arginine at residue 220.

DISCUSSION

The 1998 influenza season in South Africa was characterized by its exceptionally early occurrence as well as its severity. The first isolate from the epidemic was collected on April 9, and was identified as an influenza A H3N2 A/Sydney/5/97-like strain April 14. Thereafter the number of isolates increased sharply and peaked toward the end of May and early June. This is the earliest South African epidemic on record since influenza surveillance began in this country [McAnerney et al., 1994].

The 1998 epidemic was also particularly severe, causing widespread morbidity in the general population and significant mortality in the elderly and other high-risk individuals. Economic losses due to work absenteeism were severe while medical and pharmaceutical costs were markedly higher than during the last few winters. School absenteeism, which was used as a measure of general absenteeism, increased markedly at the height of the epidemic, resulting in the closure of several large schools in the Gauteng province.

Characterization of the 1998 H3N2 virus strains isolated during the epidemic revealed that they were antigenically distinct from the A/Wuhan/359/95 and A/Bratislava/6/97-like viruses which had circulated in South Africa the previous year. The 1998 isolates were

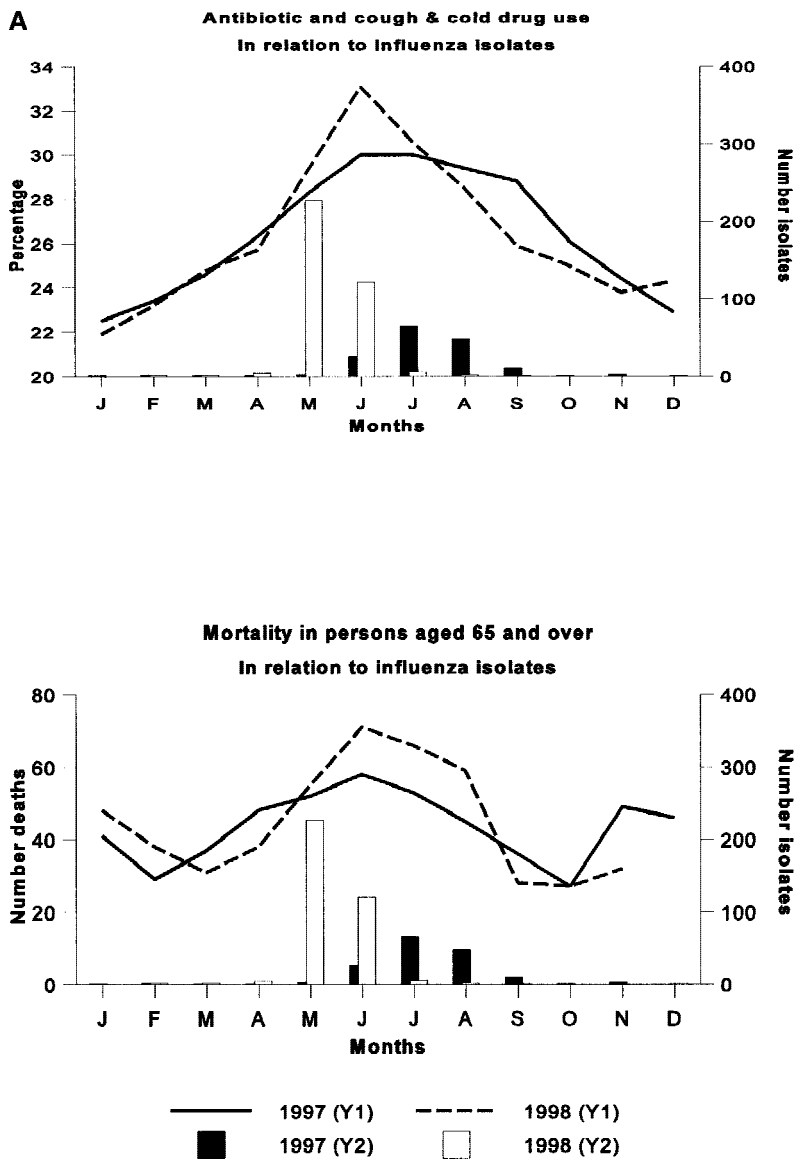

Fig. 3. Comparison of pharmaceutical use and mortality in relation to influenza isolates during 1997 and 1998. **A:** Antibiotic and cough and cold use in relation to influenza isolates. **B:** Mortality in persons aged 65 and over in relation to influenza isolates.

TABLE II. Comparison of the Amino Acid Sequence Analysis of the HA1[a] Subunit of the Preseason 1997 and 1998 H3N2 Isolates With Vaccine and Reference Strains

Virus	Substitution at AA residue in HA1[b]														
	3	62	121	124	133	142	144	156	158	194	196	220	226	275	276
A/Nanchang/933/95 vaccine strain	L	K	T	G	D	G	V	K	E	L	V	R	I	G	N
A/SA/1147/96	–	–	N	S	N	R	–	–	–	–	–	–	V	L	–
A/Jhb/1/97	–	–	N	S	N	–	–	–	–	I	–	S	V	D	–
A/Jhb/1/98	–	–	N	S	N	–	–	–	–	I	–	S	V	D	–
A/Sydney/5/97	I	E	N	S	N	S	I	Q	K	I	A	–	–	–	K

[a]The region corresponding to 78–1,000 bp of the HA1 was sequenced.
[b]Results are reported as amino acid differences between the HA1s of the isolates and that of the A/Nanchang/933/95 vaccine strain. (–), no change.

closely related to the A/Sydney/5/97 strain, a representative virus of novel variants first identified in Australia in August 1997 [Hampson and Gust, 1997]. The A/Sydney/5/97-like viruses differ extensively from the A/Wuhan/359/95-like viruses, with amino acid changes in four of the five major antigenic sites: A, B, C, and E [Hay et al., 1998].

Molecular analyses of the H3N2 viruses isolated dur-

TABLE III. Comparison of the Amino Acid Sequence Analysis of the HA1 Subunit[a] of Later 1997 H3N2 Virus Isolates With Vaccine and Reference Bratislava Strain

Isolate	Substitution at AA residue in HA1[b]							
	57	92	122	133	190	216	226	275
A/Nanchang/933/95 vaccine strain	R	K	N	D	D	N	I	G
A/Bratislava/6/97	Q	T	K	–	–	–	V	D
A/Jhb/25/97	Q	T	K	–	–	S	V	D
A/Jhb/39/97	–	T	K	N	V	S	V	D
A/Jhb/52/97	Q	T	K	–	–	S	V	D
A/Jhb/70/97	Q	T	K	–	–	S	V	D
A/Jhb/150/97	Q	T	K	–	–	S	V	D

[a]The region corresponding to 100–1,000 bp of the HA1 was sequenced.
[b]Results are reported as amino acid differences between the HA1s of the isolates and that of the A/Nanchang/933/95 vaccine strain. (–), no change.
Additional changes: A/Jhb/25/97, AA 193 (S-R); A/Jhb/52/97, AA 238 (K-T); A/Jhb/70/97, AA 248 (T-I).

TABLE IV. Amino Acid Sequence Analysis of the HA1[a] Subunit of 1998 H3N2 Virus Isolates

Isolate	Substitution at AA residue in HA1[b]									
	3	103	137	142	186	194	220	226	229	289
A/Sydney/5/97 vaccine strain	I	P	Y	S	S	I	R	I	R	P
A/Jhb/3/98	L	Q	–	R	I	L	–	–	–	–
A/Jhb/4/98	L	Q	–	R	I	–	–	–	–	–
A/Jhb/9/98	L	–	–	R	–	–	–	V	G	–
A/Jhb/13/98	L	–	–	R	–	L	–	V	G	–
A/Jhb/21/98	L	Q	–	R	–	L	–	–	–	S
A/Jhb/35/98	L	–	S	R	–	L	–	–	–	S
A/Jhb/44/98	L	–	S	R	–	–	G	–	–	–
A/Jhb/56/98	L	Q	–	R	–	L	–	–	–	S

[a]The region corresponding to 78–1,000 bp of the HA1 was sequenced.
[b]Results reported as amino acid differences between HA1s of isolates and the A/Sydney/5/97 vaccine strain. (–), no change.

ing the 1998 epidemic showed that they were A/Sydney/5/97-like. The amino acid differences between the South African isolates and the Sydney vaccine strain have been seen in many recent A/Sydney/5/97-like viruses and are thus not unique to the viruses present in this country during the epidemic. In addition, despite the slight drift away from the Sydney vaccine strain at the genetic level, the antigenicity of the isolates did not appear to be reduced as they were found to react to a high titer with the A/Sydney/5/97 antisera.

Both the preseason 1997 and 1998 virus isolates, on the other hand, shared a closer homology with the reference A/SA/1147/96 strain. This strain, isolated in Johannesburg on August 1, 1996, represents variants that are distinguishable from the A/Wuhan/359/95-like viruses by principal amino acid changes at residues 121, 124, 133, and 142. Despite the similarities between the preseason 1997 and 1998 isolates and the A/SA/1147/96 strain at residues 121, 124, and 133, antigenic drift was evident by differences observed at other amino acids occurring in the antigenic sites A, B, C, and D. These early 1997 and 1998 viruses appear to represent intermediates in the evolution of the A/SA/1147/96 and the A/Sydney/5/97-like viruses (Alan Hay, personal communication).

The first A/Sydney/5/97-like variant identified in South Africa was isolated in March 1998 from an individual who had recently visited Thailand. A significant rise in influenza A/Sydney/5/97-like viruses were detected from mid-April. With no prior exposure to these novel variant viruses, the unvaccinated population in South Africa was highly susceptible, resulting in an early, rapid spread of influenza, accompanied by severe illness and significant mortality.

Due to the virulence of the A/Sydney/5/97-like viruses in the outbreaks experienced in Australia and New Zealand in 1997, the A/Sydney/5/97 stain was chosen to replace the A/Nanchang/933/95 H3N2 strain for the 1998 Southern Hemisphere influenza vaccine [Australian Influenza Vaccine Committee, 1997].

Studies have shown that influenza vaccination can prevent illness in approximately 60%–90% of healthy adults providing the vaccines have antigenically well matched strains [Edwards et al., 1994; Centers for Disease Control, 1998]. While the efficacy of vaccination in the elderly is much lower (30%–60%), immunization does attenuate the severity of illness and reduces the incidence of life-threatening complications [Gross et al., 1995; Centers for Disease Control, 1998].

The importance of having an influenza vaccine specifically formulated for the Southern Hemisphere has been highlighted by the epidemic due to the A/Sydney-like viruses. If the 1998 vaccine had not contained the A/Sydney/5/97 strain, the epidemic in South Africa would have been much worse in terms of morbidity, mortality, and economic loss. This, in turn, emphasizes

the need for increased influenza surveillance and international cooperation.

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